REMARKS

The July 3, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

The Examiner has maintained the restriction requirement set forth previously, with the exception that plasmids pHK38 and pMSK35, pMSK45, pMSK48 and pMSK49 will be examined together. Accordingly, the Examiner indicates that claims 1-17 will be examined together, to the extent they encompass SEQ ID NO: 14. Further, the Examiner states that claims 3, 6, and 7 will be withdrawn because they do not encompass SEQ ID NO: 14. Therefor claims 1, 2, 4, 5, and 8-17 are under consideration, and have been examined to the extent that they encompass SEQ ID NO: 14.

The Examiner has objected to the black boxes in the drawings of Figures 24 and 26. Revised figures are provided herewith.

Additionally, the Examiner has required that sequence identifiers be added to page 63. The specification has been amended to in accordance with this requirement.

The Examiner has objected to claims 4, 5, 8-10, 12-14, 16, and 17, as containing minor informalities.

The Examiner has rejected claims 15-17 as allegedly failing to comply with the enablement requirement under 35 U.S.C. §112 first paragraph. The Examiner contends plasmids described thereby are inadequately enabled and require a deposit under the terms of the Budapest Treaty.

Claims 1, 2, 5, and 8-14 are rejected under 35 U.S.C. §112 first paragraph, as allegedly failing to meet the written description requirement. It is the Examiner's position that the downstream boxes of the claims are not adequately described.

Claims 1-2, 5, and 8-14 are rejected under 35 U.S.C. §112

first paragraph as allegedly lacking enablement. The Examiner contends that the claimed plastid constructs comprising downstream boxes are not enabled, because allegedly undue experimentation would be required to make and/or use the full scope of the claims which encompass downstream box elements.

The Examiner has rejected claims 1, 2, 4-6, and 8-14 under 35 U.S.C. §112 second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter of the invention.

Next, the Examiner has rejected claims 1, 2, and 5 under 35 U.S.C. §102(b). It is the Examiner's position that these claims are anticipated by Svab et al., (1993) PNAS 90:913-917 with evidence from Maliga et al, US Patent 5,877,402.

Last, the Examiner makes two rejections under 35 U.S.C. §102(e). First, claims 1, 2, 5, and 9 stand rejected as allegedly anticipated by Maliga et al, US Patent 5,877,402 with evidence from Jefferson (1993, Genbank Accession No. A00196). Finally, the Examiner rejects claims 1, 2, 5, and 9 as allegedly anticipated by McBride et al., US Patent 6,271,444, with evidence from Barry et al., US Patent 5,627,061.

The foregoing constitutes the entirety of the objections and rejections raised in the July 3, 2003 Official Action. In light of the present claim amendments and the following remarks, each of the above-noted rejections under 35 U.S.C. §§ 112, first and second paragraph, and 102(b) and (e) is respectfully traversed.

CLAIMS 4, 5, 8-10, 12-14, 16, AND 17 AS AMENDED MEET ALL FORMAL REQUIREMENTS

The Examiner has objected to claim 4-5, 8-10, 12-14, 16, and 17 for alleged informalities.

First, the Examiner indicates that claims 4, 8-10, 12-14, and 17 start with an improper article. Next, the Examiner states that claim 5 has an improper article before "DNA" in

line 1. Further, the Examiner indicates that claim 16 has an improper article before "plasmid" in line 1. Applicants respectfully submit that the claims are clear as originally recited. Nonetheless, in the interest of reducing issues for prosecution, Applicants have amended the claims to change the objected articles to "the".

Next, the Examiner indicates that claims 2 and 5 are objected to as substantial duplicates. In response to this objection, Applicants have amended claim 5 to depend from claim 4.

It is respectfully submitted that the foregoing amendments render the above-mentioned grounds of rejection moot.

CLAIMS 15-17 FULLY MEET THE ENABLEMENT REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 15-17 as allegedly lacking enablement, because the plasmids must be obtainable by a repeatable method set forth in the specification, or must be readily available to the public. If the plasmids are not so available or obtainable, a deposit is required. Applicants respectfully traverse.

The MPEP §2404 states that:

> Biological material need not be deposited, inter alia, if it is known and readily available to the public or can be made or isolated without undue experimentation.

In the instant case, the plasmids of claims 15-17 are sufficiently described in the specification so that they can be made without undue experimentation, even in the absence of a deposit. In support of this, Applicants provide herewith a description of the explicit teachings in the specification which provide methods of making the plasmids without undue experimentation.

Methods of producing plasmids pHK30 through pHK43, pHK60

and pHK64 are described at pages 23-40. Pages 23-24 describe determination of downstream box regions; pages 24-30 describe the design of a leader sequence; and pages 31-39 describe construction of the chimeric Prrn promoter with leader sequence. Table 1 at page 25 describes the specific components of the 5' regulatory regions, as well as which plastid transformation vector each 5' regulatory region is incorporated into. The plasmid names are provided in the far right column, with their corresponding transformation vector in parentheses. The regulatory region can be determined from the first and third columns. Specifically, the nomenclature for all of the regulatory regions begins with the rRNA operon σ^{70}-type promoter (Prrn) followed by the leader (L) (first column, Table 1) and then the type of downstream box (DB; third column, Table 1). As an example, the plasmid pHK30 would be determined from Table 1 to have a regulatory region consisting of (Prrn), (LatpB), and (+DBwt) or PrrnLatpB+DBwt as listed in Group I, which is incorporated into pPRV111B. The sequences of all of these regulatory regions are shown in Figures 3A-3D; the site of incorporation into the respective vectors is shown in Figures 4A-B. Pages 39-40 describe the cloning of the 5' regulatory regions upstream of the neo gene. The sequence of the neo gene is shown in Figure 9. These chimeric neo genes were cloned into pPRVIIIA and pPRVIIIB vectors to create plasmids pHK30 through pHK43, pHK60 and pHK64. The pPRVIIIA and pPRVIIIB vectors are described at page 30, lines 16-29, and are disclosed in US Patent 5,877,402, which is incorporated by reference. Furthermore, these plasmid sequences have also been deposited with Genbank, Accession Nos, U12812 and U12813, respectively.

As noted by the Examiner, the sequences of plasmid pMSK49 are shown in Figures 34A-B. Applicants respectfully submit that pMSK35 is similarly shown in Figures 33A-B. Plasmids pMSK45, pMSK48, pMSK53, pMSK54, pMSK56, and pMSK57 are derivatives of these plasmids, and methods of making these

plasmids are described at pages 79-85. Specifically, plasmids pMSK53 and pMSK54 contain the regulatory regions PrrnLrbc+DBwt and PrrnLatpB+DBwt, respectively, operably linked to the aadA16gfp gene, whose sequence is shown in Figure 28 (see page 79, lines 4-20). As noted at page 79, lines 21-26, pMSK57 and pMSK56 are generated by excising EcoRI-SpeI fragments of pMSK53 and pMSK54 and inserting the fragments into a similarly digested pRVIIIB plasmid (see also page 84, line 22 to page 85 line 3 and Figures 29 and 30). At page 80, line 26 to page 81, line 16, the components of plasmids pMSK45 and pMSK48 are characterized. pMSK45 is a derivative of pMSK35 which carries the PrrnLT7g10+DB/Ec promoter controlling a kanamycin resistance gene. pMSK48 is generated by cloning *gfp* and *aadA* from plasmid pMSK41 into pMSK45 via an NheI-HindIII digestion.

In summary, in light of the extensive disclosure of the structure and sequences present in the plasmids of claims 15-17, as well as methods of making the same, the skilled person could readily generate such plasmids without undue experimentation. Accordingly, a deposit is not required to practice the full scope of the invention.

CLAIMS 1, 2, 5, AND 8-14 FULLY MEET THE WRITTEN DESCRIPTION REQUIREMENTS OF 35 U.S.C. § 112 FIRST PARAGRAPH

Claims 1, 2, 5, and 8-14 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the written description requirement. Applicants respectfully maintain, however, that the present specification includes written description more than sufficient to meet the statutory requirement. At the outset, the requirements for written description are detailed in the MPEP at § 2163,

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Furthermore, the written description guidelines set forth in the Federal Register Vol. 66, No. 4, January 5, 2001 state that "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention."(page 1105, column 3). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, ie: complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." (Page 1106, column 1).

The Examiner cites *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) as support for her contention that the claims lack written description. In *University of California V. Eli Lilly and Co.*, the courts ruled that disclosure of a process for obtaining cDNA from a particular organism and description of the encoded protein failed to provide written description of the actual cDNA from the organism which would encode the disclosed protein, despite the disclosure of a cDNA encoding that protein from another organism. The court also addressed the manner by which a genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Applicants submit that the fact pattern in the instant case is very different from that in the *University of California V. Eli Lilly and Co.* In the Lilly case, the claimed

subject matter was never described. However in the instant case, a multiplicity of downstream box elements are described. Thus the instant application meets the standards for description set by *University of California V. Eli Lilly and Co.*, and as well as the interim guidelines for written description, because the instant case provides sequence information for a "reasonable number" of downstream box elements, and further provides structural and functional information about all of the claimed downstream box elements.

For example at page 3, lines 3-11, exemplary bacterial downstream box elements are described. Further, at pages 23-24, the specification teaches methods of determining a plastid downstream box element, including structural and functional information. Figures 1A and 2A-2B, depict exact sequence information for exemplary downstream box elements, and show the structure (size and complementarity) of these downstream box elements. Additionally, Figures 3A-3D show the sequences of numerous chimeric 5' regulatory regions which all comprise downstream box elements. Therefore the specification describes many specific downstream box element sequences, provides guidelines for determining other downstream box elements, such as complementarity to anti-downstream box regions, and provides a specific function associated with downstream box elements (i.e., enhanced translational efficiency.)

This combination of teachings meets the requirements for written description described above, as a representative number of downstream box elements, as well as the general structure, and function of the downstream box is clearly disclosed, along with exemplary means of identifying a downstream box. Accordingly, Applicants submit that the claims are adequately described, and request withdrawal of the rejection.

CLAIMS 1, 2, 5, AND 8-14 FULLY MEET THE ENABLEMENT REQUIREMENTS OF 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner has rejected claims 1, 2, 5, and 8-14 as allegedly lacking enablement. Applicants respectfully traverse.

It is the Examiner's position that the specification does not enable the full scope of claims which comprise downstream boxes for use in 5' regulatory regions that enhance translation efficiency of an mRNA.

However, as set forth above, the structure and function of a plastid downstream box is clearly described, and numerous specific downstream boxes are disclosed in the specification. Therefore, from the teachings of the specification, it would require only routine experimentation to determine additional putative downstream box elements and test the same to determine their effect on translational efficiency.

With regard to the Examiner's assertion that one of ordinary skill in the art would not be able to practice the invention without undue experimentation, the Examiner's attention is respectfully directed to MPEP §2164.06, which discusses quantity of experimentation necessary with regard to enablement:

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given direction or guidance." In re Colianni, 561 F.2d 22, 224, 195 USPQ 150, 153 (CCPA 1977)"'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir 1988) (citing In re Angstadt, 537 F.2d 489, 502-504, 190 USPQ 214, 217-219 (CCPA))

Also, in Example B, under the heading "SEVERAL DECISIONS RULING THE DISCLOSURE WAS ENABLING", MPEP §2406.6(b) cites a specific example of a biotechnology case in which a large amount of experimentation (likely far more than would be required in the instant case) was found **NOT** to be undue:

> (B) In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir 1988), the court reversed the rejection for lack of enablement under 112 first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make the monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, applicant carried out the entire procedure for making a monoclonal antibody against HbsAg three times and each time was successful in producing at least one antibody which fell within the scope of the claims.

Applicants respectfully submit that use of conventional techniques in genetic engineering would allow a skilled artisan to develop constructs containing the putative downstream domains and then subsequently screen the constructs for enhanced translational efficiency. Exemplary techniques are outlined throughout the specification, particularly at pages 23-25, which describe downstream box element identification, construction, and screening. Further, Examples I-VIII all describe methods of constructing vectors comprising putative downstream box elements and determining translational efficiency as a function of reporter gene expression levels operably linked thereto.

In light of the evidence and argument presented herewith, Applicants respectfully submit that the invention is fully

enabled and request the withdrawal of the §112, first paragraph rejection of claims 1, 2, 5, and 8-14.

CLAIMS 1, 2, 4-6, AND 8-14 AS AMENDED FULLY MEET THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected claims 1, 2, 4-6, and 8-14 as allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants respectfully traverse.

It is well established that claims are not indefinite when they have a reasonable degree of particularity and distinctness, such that the metes and bounds of the invention are clear to those of skill in the art. See, e.g., MPEP § 2173.02.

First, the Examiner states that claim 1 is indefinite for the recitation of "higher plants". Applicants respectfully traverse this rejection. It is submitted that the skilled artisan would readily recognize that a higher plant refers to any multicellular plant organism. "Higher plant" is a well recognized term of art, known to refer to plants which produce seeds, such as angiosperms or gymnosperms. Further in evidence of this is the inclusion of the term in the USPTO Classification system (class 800, subclass 298; Subject matter wherein the plant, seedling, plant seed, or plant part is a higher plant, i.e., an angiosperm or gymnosperm. See attached classification schedule from www.uspto.gov.) It is a well-settled premise in patent law "that a patent need not teach, and preferably omits, what is well known in the art". Lindemann Maschinenfabrik v. American Hoist and Derrick, 221 U.S.P.Q. 481 (Fed. Cir. 1984). Accordingly, Applicants submit that the metes and bounds of "higher plant" are clear.

Next, the Examiner is unclear as to what the term "heterologous" is modifying in claim 1. Applicants respectfully submit that the term heterologous in claim 1 refers to a protein which is heterologous to the plant, i.e.,

derived from a different source. The different source, in this case, is the construct which contains the coding sequence for the heterologous protein of interest (which can be any protein sequence). The definition of heterologous and heterologous gene expression from The Encyclopedia of Molecular Biology, is submitted herewith and evidences that the skilled person would be readily apprised of the metes and bounds of the term in the claims.

It appears that the rejection is premised on the fact that the claim can encompass any heterologous protein, and thus it appears that the Examiner objects to the breadth of the claim. This is not proper under §112, second paragraph. See M.P.E.P. §2173.05:

> **-Breadth is Not Indefiniteness-**
> Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. §112 second paragraph.

The fact that "heterologous" may refer to any number of proteins does not make the term vague and indefinite. Accordingly, Applicants request withdrawal of the rejection.

Next the Examiner has indicates that the term "enhancing" in claim 1 is a relative term and is therefor indefinite. The claim has been amended to recite the enhancement is relative to translational efficiency of constructs which lack the chimeric promoter region. Furthermore, Applicants respectfully submit that the present application expressly discloses that incorporation of the down stream box elements in the instantly claimed constructs and plasmid give rise to increased levels of reporter gene expression relative to constructs that lack such elements. In light of the above amendment and remarks, Applicants respectfully submit that this recitation is clear.

The Examiner also states that claims 1, 8, and 13 lack antecedent basis in the recitation of "said chimeric regulatory region" in claim 1, "said synthetic bar nucleic acid" in claim 8 and "said aadA coding region" and "said green fluorescent protein coding region" in claim 13. Applicants respectfully submit that it is clear what the cited phrases refer to. However, in the interest of furthering prosecution, Applicants have amended claims 1 and 8 to provide literal antecedent basis and have amended the dependency of claim 13 in accordance with the Examiner's helpful suggestion.

The Examiner rejects claim 4, indicating that it is not clear if the Markush group has six or three members. Applicants have amended claim 4 to recite the chimeric promoter element of SEQ ID: NO 14, thereby obviating this objection.

The Examiner also states that claims 8, 13, and 14 are unclear for the recitation of the term "having." The Examiner states that the term "having" is unclear because it is not clear if "having" is open language or closed language. Applicants respectfully submit that the term "having" is known to refer to open language. In the interest of expediting prosecution, however, Applicants have amended claims 13 and 14 to recite "comprising" in place of "having" and claim 8 to recite "is" in place of "having."

Next, the Examiner indicates that claim 10 is indefinite for the recitation of "said fusion protein having a first and second coding region", because proteins do not have coding regions. Applicants respectfully submit that it is clear that coding region refers to the nucleic acid which encodes the fusion protein. The Examiner also indicates that it is not clear if the nucleic acid encoding the fusion protein is comprised of two operably linked coding regions, or if the fusion protein is encoded by more than one coding region. Again, Applicants submit that the components of the fusion protein, and the nucleic acid encoding it are clear from the

claim as originally recited. Nonetheless, Applicants have amended the claim to further clarify the metes and bounds of the subject matter encompassed thereby.

The Examiner states that claim 10 is indefinite in the recitation of "said first coding region encoding a selectable marker gene", because coding regions do not encode genes. Applicants respectfully submit that the recitation "said first coding region encoding a selectable marker gene" clearly refers to a coding region which encodes a selectable marker. Nonetheless, Applicants have amended the claim to more clearly set forth the subject matter encompassed by this claim.

Next, the Examiner rejects claim 12 for the recitation of "said fusion protein consisting of an aadA coding region operably linked to a green flourescent protein coding region", because proteins do not have coding regions. Applicants have amended the claim to recite a polynucleotide which comprises these coding region thereby rendering this objection moot.

With regard to the Examiner's assertion that the sequences of the Markush group in claim 14 are "very different sequences", Applicants respectfully submit that all of the sequences refer to all or part of a plasmid system which enhances translational efficiency. Thus, the constructs are all related members. Applicants also submit that members of a Markush group do not need to be equal, as the Examiner implies.

Applicants note that the Examiner lists claims 1, 2, 4-6, and 8-14 as being rejected under 35 U.S.C. §112, second paragraph as indefinite, yet claim 6 has been withdrawn and no explanation as to how claims 2, 5, 9 and 11 are indefinite has been provided by the Examiner. Applicants respectfully request clarification.

In view of the amendments presented herewith and the foregoing remarks, Applicants respectfully request the withdrawal of the rejection of claims 1, 2, 4-6 and 8-14 under 35 U.S.C. §112, second paragraph.

CLAIMS 1, 2, AND 5 ARE NOVEL OVER SVAB ET AL., WITH EVIDENCE FROM US PATENT 5,877,402

The Examiner has rejected claims 1, 2, and 5 under 35 U.S.C. §102(b) as allegedly anticipated by Svab et al.(PNAS (1993) 90:913-917) with evidence from US Patent 5,877,402. Applicants respectfully traverse.

MPEP §2131 sets forth the standard for a 102 rejection:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants submit that the teachings of Svab et al. do not meet all of the limitations of the claims. The constructs of Svab et al. do not comprise a chimeric 5' regulatory region comprising a downstream box element which is operably linked to a coding region of a heterologous protein.

The Examiner has used homology alignments to indicate that the aadA gene of Svab et al. contains a downstream box element. Applicants submit, however, that this identification of potential downstream boxes does not meet the limitations of the instant claims. Indeed, claim 1, from which claims 2 and 5 depend, describes a recombinant DNA construct which comprises a "chimeric 5' regulatory region which includes a promoter element, a leader sequence and a downstream box element **operably linked** to a coding region of" a heterologous protein. As defined at page 9, lines 11-14, operably linked refers to two different regions spliced together. This is not the case in the Svab et al. reference, which contains an alleged downstream box element **within** the coding region of the heterologous protein. Therefore, Svab et al. fail to disclose a **chimeric** regulatory region that contains a downstream box element operably linked to a region encoding a heterologous

protein.

Applicants also submit that the instantly claimed invention requires that the chimeric regulatory region enhance translational efficiency. Svab et al. are silent as to whether the downstream box elements present in the aadA coding region increase translation efficiency relative to plasmids which lack such sequences.

Inasmuch as Svab et al. fail to describe each and every element of the claimed invention, Applicants respectfully request the rejection of claim 1, 2, and 5 under 35 U.S.C. §102(b) be withdrawn.

CLAIMS 1, 2, 5, AND 9 ARE NOVEL OVER US PATENT 5,877,402 WITH EVIDENCE FROM JEFFERSON

The Examiner has rejected claims 1, 2, 5, and 9 under 35 U.S.C. §102(e) as allegedly anticipated by US Patent 5,877,402 (Maliga et al.) with evidence from Jefferson (1993, Genbank Accession No. A00196). Applicants respectfully traverse.

Applicants submit that the teachings of the '402 patent do not meet all of the limitations of the claims. The constructs of the '402 patent do not comprise a chimeric 5' regulatory region comprising a downstream box element which is operably linked to a coding region of a heterologous protein.

The Examiner has used homology alignments to indicate that the aadA, uidA, and kan genes of the '402 patent contain a downstream box element. Applicants submit, however, that this identification of potential downstream boxes does not meet the limitations of the instant claims.

As noted hereinabove, the claimed invention requires a chimeric 5' regulatory region operably linked to a region encoding a heterologous protein, wherein the regulatory region contains promoter, leader, and downstream box elements. The 402' patent fails to teach or describe a chimeric 5' regulatory region comprising a downstream box element, which is operably linked to, and increases expression of a

heterologous protein. Indeed, the construct in the '402 patent cited by the Examiner contains an alleged downstream box element **within** the coding region of the heterologous protein and is therefore not apart of the 5' regulatory region operably linked to the heterologous protein.

Furthermore, Applicants submit that the '402 patent is not "by another," because the patent is Applicant's own work. Applicants are willing to submit a showing under 1.132, should the Examiner require such evidence.

In view of the foregoing remarks, Applicants respectfully request the withdrawal of the rejection of claims 1, 2, 5, and 9 under 35 U.S.C. §102(e).

CLAIMS 1, 2, 5, AND 9 ARE NOVEL OVER US PATENT 6,271,444 WITH EVIDENCE FROM US PATENT 5,627,061

The Examiner has rejected claims 1, 2, 5, and 9 under 35 U.S.C. §102(e) as allegedly anticipated by US Patent 6,271,444 (McBride et al.), with evidence from US Patent 5,627,061 (Barry et al.). Applicants respectfully traverse.

Applicants submit that the teachings of the '444 patent do not meet all of the limitations of claims 1, 2, 5, and 9. The constructs of the '444 patent do not comprise a chimeric 5' regulatory region comprising a downstream box element which is operably linked to a coding region of a heterologous protein.

The Examiner has again used homology alignments to indicate that the Rubsico/EPSPS gene of the '444 patent contains a potential downstream box element. As noted hereinabove, the instantly claimed invention requires a chimeric 5' regulatory region comprising a downstream box element, which is operably linked to, and increases expression of a heterologous protein. The construct in the '444 patent cited, however, contains an alleged downstream box element within the coding region of the heterologous fusion protein.

Therefore, the downstream box element in the '444 patent is not part of the 5' regulatory region and is not operably linked to the heterologous protein as defined in the instant application.

Inasmuch as the '444 patent fails to describe each and every element of the claimed invention, Applicants respectfully request the rejection of claim 1, 2, 5, and 9 under 35 U.S.C. §102(e) be withdrawn.

CONCLUSION

In view of the amendments and remarks presented herein, it is respectfully urged that the rejections set forth in the July 3, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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Enclosures: Definition of Heterologous
Patent classification system as it relates to higher plants
Amended Figures 24 and 26

295	**PLANT, SEEDLING, PLANT SEED, OR PLANT PART, PER SE**
296	. Multicellular algae
297	. Mushroom
298	. Higher plant, seedling, plant seed, or plant part (i.e., angiosperms or gymnosperms)
299	.. Haploid
300	.. Herbicide resistant plant which is transgenic or mutant
300.1	... The plant is maize
301	.. Pathogen resistant plant which is transgenic or mutant
302	.. Insect resistant plant which is transgenic or mutant
303	.. Male-sterile
304	.. Somatic cell fusion product or somatic cell fusion-derived plant
305	.. Lettuce
306	.. Brassica
307	.. Cucumber
308	.. Watermelon
309	.. Melon (e.g., cantaloupe, honeydew, etc.)
310	.. Squash (e.g., pumpkin, zucchini, etc.)
311	.. Pelargonium
312	.. Soybean
313	.. Bean
314	.. Cotton
315	.. Apple
316	.. Citrus (e.g., orange, lemon, lime, etc.)
317	.. Solanaceae (e.g., eggplant, etc.)
317.1	... Pepper

317.2	... Potato
317.3	... Tobacco
317.4	... Tomato
318	.. Celery
319	.. Conifer
320	.. Gramineae (e.g., barley, oats, rye, sorghum, millet, etc.)
320.1	... Maize
320.2	... Rice
320.3	... Wheat
321	.. Lily
322	.. Sunflower
323	.. Ornamental plant
323.1	... Petunia
323.2	... Chrysanthemum
323.3	... Carnation

THE ENCYCLOPEDIA OF Molecular Biology

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Blackwell Science

h ritability Statistical measure of the degree to which a phenotypic trait (including a disease) is genetically determined. Many traits have both genetic and environmental components.

H rp sviridae A family of animal DNA viruses (*see* ANIMAL VIRUSES). They include the type 1 and 2 herpesviruses, the varicella-zoster virus, which causes chickenpox and shingles, the EPSTEIN-BARR VIRUS and cytomegalovirus. Type 1 herpesvirus causes cold sores, type 2 is associated with genital lesions, and types 1 and 2 have been implicated in human cancers. The mature virion is 100–180 μm in diameter and enclosed in a double membrane. The viral capsid is ICOSAHEDRAL and composed of 162 capsomers. Genome size varies from 120–200 kb, encoding around 50 genes. Genome organization varies between different members of the family. In the herpesviruses, the genome consists of two parts separated by inverted repeats. Recombination between the repeats at the ends of the genome and the internal inverted repeats gives rise to different forms of the genome in which one or both of the parts have become inverted. Herpesviruses multiply inside the nucleus of the host cell. Three classes of genes (α, β, and γ) have been identified which are expressed very early, early, and late (after DNA replication) during infection.

h tero-oligomeric Applied to proteins composed of different types of subunit. Applied for example to members of the LIGAND-GATED ION CHANNEL SUPERFAMILY. *See*: EXCITATORY AMINO ACID RECEPTORS; GABA AND GLYCINE RECEPTORS; NICOTINIC RECEPTOR. *Cf.* HOMO-OLIGOMERIC.

h terochromatin *See*: CHROMATIN.

h terochronic mutations Mutations that alter the timing of developmental events. The nematode (*Caenorhabditis elegans*) is particularly useful for studies of mutation which cause heterochrony because the lineages of all the cells in the adult are known and are more or less invariant among normal individuals. Heterochronic mutations in *C. elegans* cause accelerated or retarded development of particular cell lineages or whole larvae. For example, the mutation *lin-14* causes cells to differentiate early, skipping the divisions that normally occur in the first larval stage. The mutation *lin-4* delays differentiation by causing lineages to reiterate the divisions which give rise to the first larval stage. It has been proposed that these kinds of mutations may also be important in an evolutionary perspective for establishing differences in behaviour and anatomy between closely related species. *See also*: CAENORHABDITIS DEVELOPMENT.

heterochrony A term used in evolutionary genetics to describe the change in onset of a particular developmental process so that the growth rate of a particular feature is changed in a descendant relative to an ancestor.

heteroclitic antibody An ANTIBODY induced to one antigenic determinant that binds with higher affinity to a different, but usually structurally related, determinant.

h t r cyst Specialized nitrogen-fixing cells produced by CYANOBACTERIA of Sections IV and V of the classification of Rippka et al. Some other genera can fix nitrogen without forming heterocysts. Heterocysts are characterized by the synthesis of a thick envelope, the induction of nitrogenase synthesis and the loss of photosynthetic oxygen evolution. Differentiation is associated with a genetic rearrangement, which activates nitrogenase synthesis.

Rippka, R. et al. (1979) *J. Gen. Microbiol.* **111**, 1–61.

heterodimer Protein made up of two different polypeptide chains, associated either covalently or noncovalently.

Heterodontus fransci Horned shark. *See*: GENERATION OF DIVERSITY.

heteroduplex A hybrid duplex nucleic acid (usually DNA) formed by the annealing of two partially or totally complementary polynucleotide chains derived from different parental molecules. Heteroduplex DNA is formed naturally at the point of RECOMBINATION between homologous chromosomes.

heteroimmune *See*: LAMBDA.

heterokaryon A single cell, syncytium, or multinucleate fungal mycelium which contains HAPLOID nuclei of two or more different GENOTYPES within the same common cytoplasm. Heterokaryons are formed when the haploid hyphal cells of certain filamentous fungi fuse to produce a single cell with an $n+n$ PLOIDY as opposed to the diploid $2n$ generated by KARYOGAMY. Heterokaryons can break down to produce haploid cells. The heterokaryon test can be used to confirm the CYTOPLASMIC INHERITANCE of a genetic trait (e.g. genetic traits determined by mitochondrial genes).

heterologous Derived from a different source, applied for example to: ANTIBODIES raised against proteins of another species; a GENE introduced into a cell of a different species or type from that of its original source.

heterologous gene expression systems A system (*in vivo* or *in vitro*) enabling the expression of a gene in a species or cell type different from that from which it was originally isolated. *See e.g.*: EXPRESSION VECTORS; GENETIC ENGINEERING; IN VITRO TRANSLATION; PLANT GENETIC ENGINEERING; TRANSGENIC TECHNOLOGY; XENOPUS OOCYTE EXPRESSION SYSTEM.

heterophilic binding Binding of one molecule to another different molecule. Applied to the binding of adhesion molecules. *Cf.* HOMOPHILIC binding.

heterosis The phenomenon of greater FITNESS and survival of hybrid organisms, particularly those formed by crossing highly inbred lines. Heterosis is usually a reflection of an increased HETEROZYGOSITY, and the increased vigour is thought to be due to the masking of RECESSIVE ALLELES deleterious in the HOMOZYGOUS state.

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